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Editors' Statement

Ruzicka, Doehner & Rousselot: Portal Venography: Anatomic and Physiologic Considerations in Interpretation

Schneider & Clark: Hyperchlorhydria Induced by Intravenous Reserpine

Riese: Prantal in Long-Term Anticholinergic Therapy

Texter: Medical Grand Rounds: Hirschsprung's Disease

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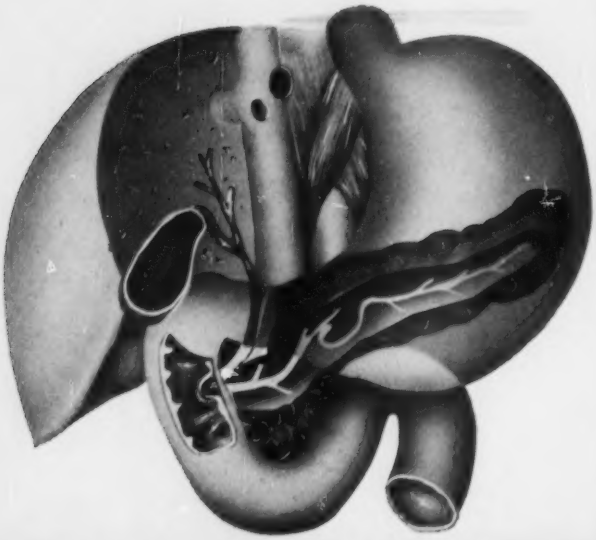

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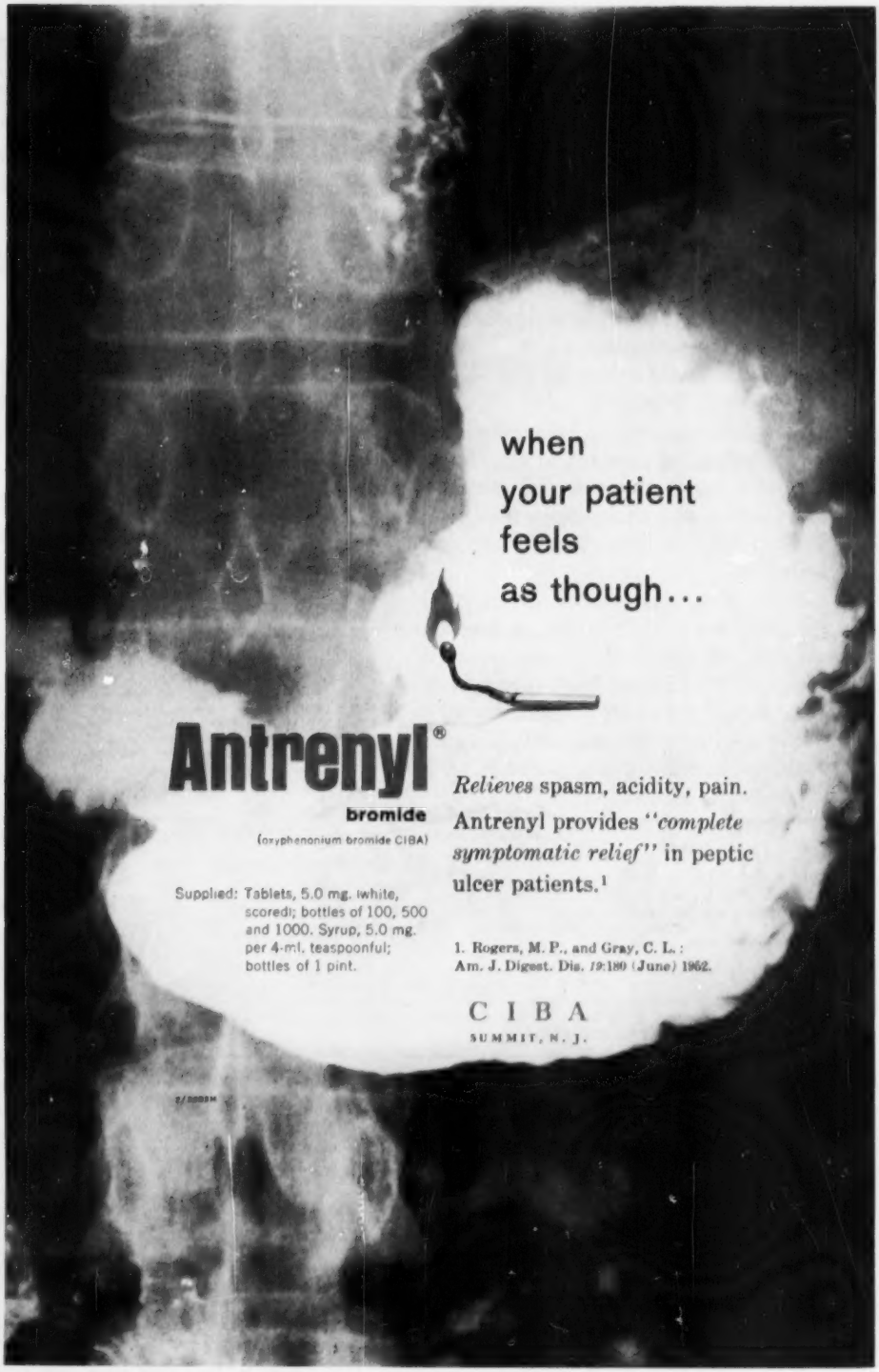
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1. Rogers, M. P., and Gray, C. L.: Am. J. Digest. Dis. 19:180 (June) 1952.
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Pork in the Human Dietary

PORK MAY be looked upon as an important factor in America's general health and well-being. The average intake of pork in America is about 46 pounds of lean pork and 20 pounds of bacon and salt pork per person each year.[1] But America's demand for pork goes further than taste appeal and deeper than mere statistics. Pork makes a valuable contribution to day-in-and-day-out nutrition.

Pork rates among the foremost sources of thiamine. As a source of all other B vitamins and many essential minerals, such as iron and phosphorus, pork meat is considered an important dietary constituent.

Lean pork is virtually completely digestible. Its protein serves to promote growth and aid in the maintenance of tissue cells. Like all high quality protein, that of pork aids in the elaboration of protein hormones, enzymes, and antibodies.

Pork constitutes a valuable part of the daily diet (Table I), and also contributes importantly to the nutrition of the pregnant woman (Table II).

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1. Consumption of Food in the United States, 1909-1952, Washington, D.C., United States Department of Agriculture, Bureau of Agricultural Economics, Agricultural Handbook No. 62, September, 1953.
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8. Recommended Dietary Allowances, Washington, D.C., National Academy of Sciences—National Research Council, Publication 302, 1953.

Cooked Pork Chops, Ham, and Pork Sausage
Nutrients and Calories Provided by 3-Ounce Portions

TABLE I	Protein Gm.	Thiamine mg.	Niacin mg.	Riboflavin mg.	Iron mg.	Phosphorus mg.	Calories
Pork Chops, without bone, cooked, 3 oz.[2]	20	0.71	4.3	0.20	2.6	200	284
Ham, without bone, cooked, 3 oz.[2]	20	0.45	4.0	0.20	2.6	202	338
Pork Sausage, cooked, 3 oz.[3]	14	0.42	2.8	0.20	2.1	139	396

3.5 ounces of fresh pork loin, equivalent to approximately 3 ounces of cooked loin, contains 0.47 mg. pantothenic acid;[4] 0.10 mg. pyridoxine;[4] 0.005 mg. biotin;[5] 36 mg. inositol;[4] 0.08 mg. folic acid;[4] 0.0027 mg. vitamin B_{12};[6] 63 mg. chlorine;[7] 0.1 mg. copper;[7] 20 mg. magnesium;[7] 280 mg. potassium;[7] 70 mg. sodium;[7] and 0.01 mg. manganese.[7]

Nutrients and Calories of Cooked Pork Chops (3 ounces) Expressed as Percentages of Recommended Daily Dietary Allowances[8]

TABLE II Percentages of Allowances for:	Protein	Thiamine	Niacin	Riboflavin	Iron	Phosphorus	Calories
Girls, 13-15 years of age; weight, 108 lb.; height, 63 inches.	25%	55%	33%	10%	17%	15%	11%
Women, 25 years of age; weight, 121 lb.; height, 62 inches.	31%	59%	36%	14%	22%	17%	12%
Pregnant Women (3rd trimester)	25%	47%	29%	10%	17%	13%	11%

The nutritional statements made in this advertisement have been reviewed by the Council on Foods and Nutrition of the American Medical Association and found consistent with current authoritative medical opinion.

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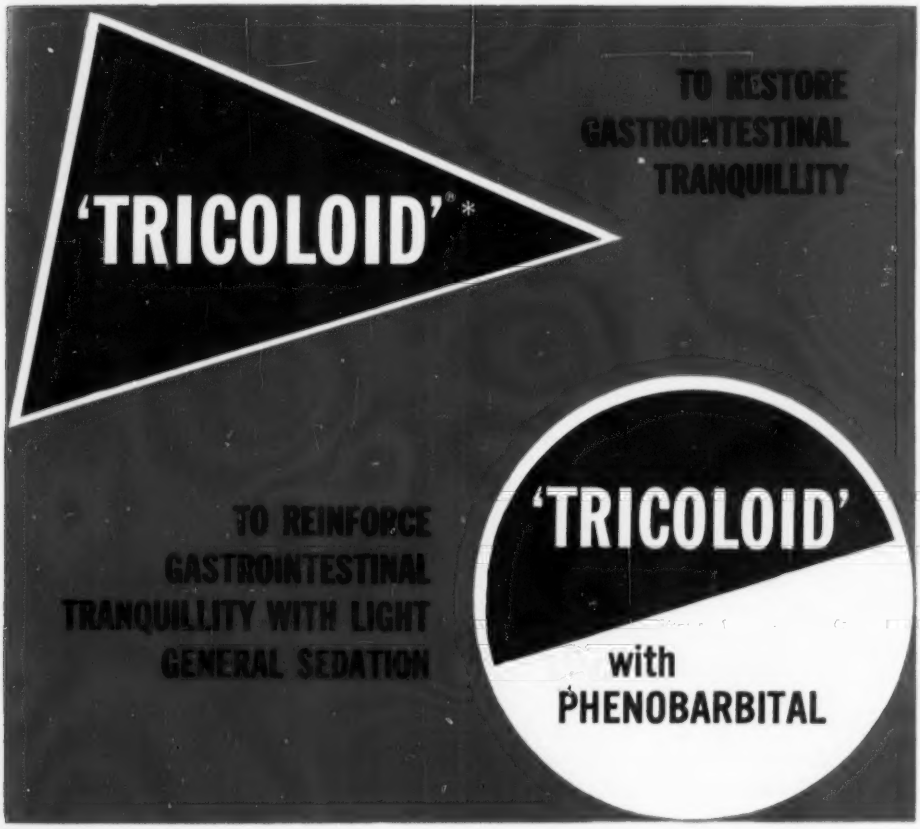

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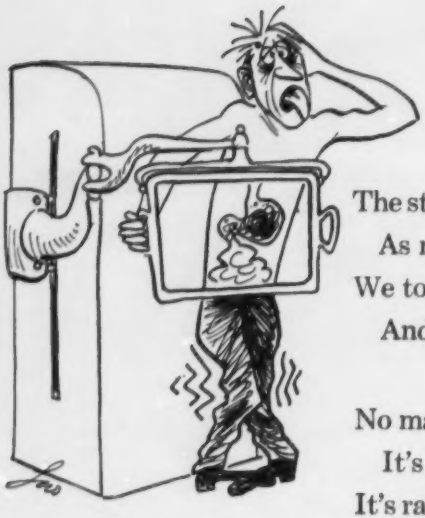

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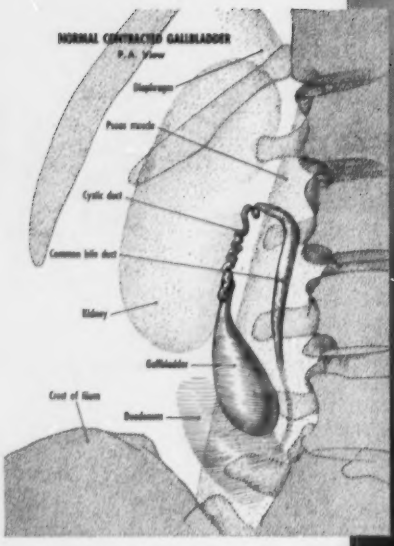

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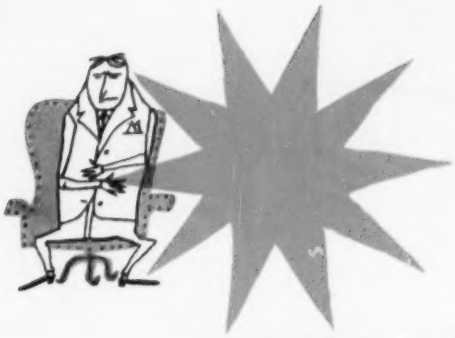

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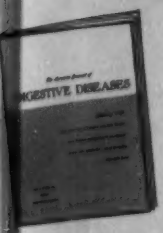

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Editors' Statement

With this issue The American Journal of Digestive Diseases passes into the hands of a new publisher and a new editorial board. In recognition of the many changes taking place both in content and in format Volume numbering will begin afresh and the January, 1956, issue will be known as New Series: Volume 1, Number 1.

On assuming responsibility for the future course of America's pioneer journal in gastroenterology, we feel a responsibility to define our concept of this field of medicine and the role of publication in it.

Gastroenterology is a major area of medicine. A rough survey at a large general hospital recently indicates that from 25 to 30 per cent of the patients have disturbances in function or structure of the gastrointestinal tract and related digestive glands. It seems likely that the proportion would run about the same in private general practice.

The need for more fundamental scientific research in disorders of the gastrointestinal tract is widely recognized. Gastric cancer, for example, now the most urgent problem requiring fundamental attack, cannot be approached solely as a problem in cancer research but must be investigated in terms of specific gastric pathophysiology. The increasing concentration on the pernicious anemia-cancer relation reflects this new attitude. Among unsolved clinical problems awaiting concerted attack are those of small-bowel absorption and intestinal inflammatory disease. Ulcerative colitis remains a challenge. There is imperative need for accurate evaluation of current gastrointestinal therapies.

Many responsible individuals and organizations are grappling with the complex problem of stimulating that basic research which has dramatically advanced so many related branches of medicine in recent years. Communication between original minds at the level of basic-science research is properly the role of the specialty journal, and our field is fortunate in already possessing such a medium of highest caliber.

Need for Clinical Journal

However, there remains a very pressing unfilled need for a medium to translate and communicate the growing accumulation of scientific information to those clinicians responsible for the active care and treatment of patients.

Editor's Statement

The new AMERICAN JOURNAL OF DIGESTIVE DISEASES is dedicated to meeting this need. It is intended as a medium for the prompt publication of scientific studies and didactic reports for those actively engaged in clinical practice. It is our hope that our colleagues, wherever situated, will utilize these pages for needed and periodic progress reports in gastroenterology.

Scope of The Journal

The Editors conceive of gastroenterology in its widest sense as being intimately related to the entire field of internal medicine and surgery, in which it developed historically. The scope of the Journal, therefore, is clinical gastroenterology broadly defined, including disorders of the liver and disturbances in nutrition and metabolism as they relate to the gastrointestinal tract. We hope that the Journal will serve as a meeting place for the great variety of disciplines involved, for cross-fertilization between clinician, biochemist, surgeon, radiologist, psychiatrist, physiologist, and nutritionist. The borderlines of gastroenterology are fruitful areas for discussion, and appropriate symposia are planned to this end.

It is intended that the Editorial Board will reflect these various approaches to clinical gastroenterology, and additional appointments will be announced in coming months to round out our program. The importance of diagnostic roentgenology is recognized by the presence of several radiologists on the board. Every effort will be made to provide faithful reproductions of x-ray films. The clinical value of new technics in radiology is demonstrated in this issue by the paper on visualization of the portal venous system by Ruzicka, Doehner, and Rousselot.

To achieve the objectives set for ourselves we plan to employ the widest range of technics available to modern medical journalism. Readers will find here, in addition to original contributions, such special editorial features as reports of medical grand rounds from leading centers, clinical-pathologic conferences, seminars, and review articles. From time to time a special issue will be devoted to a symposium on a specific topic of timely clinical concern.

In short, the Editors hope to provide a journal which will prove both valuable and interesting to the physician and surgeon in the active practice of medicine. To this end we bespeak the support and cooperation of their colleagues and friends throughout the profession.

THE EDITORS

Portal Venography

Anatomic and Physiologic Considerations in Interpretation

FRANCIS F. RŮZICKA, JR., M.D., GUENTHER A. DOEHNER, M.D., and LOUIS M. ROUSSELOT, M.D.

ROENTGEN examination of the portal venous system has now reached such a stage of development that its application in certain cases results not only in useful but at times vital information concerning the disease process under study. For adequate interpretation of the findings in a roentgen examination the anatomy and physiology of the portal system, both normal and abnormal, must be understood. It is a discussion of these fundamentals as applied to portagraphy* with which this paper is concerned.

Technics of portal venography have been described in detail elsewhere,[2, 6, 7] and need be mentioned here only in passing. Splenic portagraphy, by far the most popular method, since it can be performed without surgery, is accomplished by injection of contrast medium into the spleen (actually into the sinuses) after percutaneous insertion of a needle through the lateral thoracic wall. Portal portagraphy, which consists of injection of a cannulized vein at laparotomy, is also useful, especially in cases where splenectomy has previously been performed or where technical failures with the splenic portagram have occurred and where it is important to obtain information concerning the portal system. This technic is useful as a supplement to the splenic portagram. At times the portal portagram will show certain collateral veins better than or in addition to the veins and systems demonstrated in the splenic portagram (the reverse also holds true). This is related to certain factors which influence the visualization of collaterals in a given instance. They will be discussed later in some detail. It is quite possible

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Presented at a meeting of the New York Roentgen Society, November 21, 1955, New York, N. Y.

* This relatively new word has been spelled variously *portagraphy* and *portography*. Since the preparation of this paper it has become apparent that the latter will be preferred.

that employment of serial filming may reveal the additional information that the combined technic of single-exposure splenic portagraphy and portal portagraphy offers.

INFORMATION DERIVED FROM PORTAGRAPHY

Normal Anatomy and Physiology

Textbooks of anatomy show as a rule a fairly fixed pattern of the portal venous tree. There are, however, a number of variations in position of the various vessels, knowledge of which is important in the proper identification of these vessels in the roentgenogram. Thus,

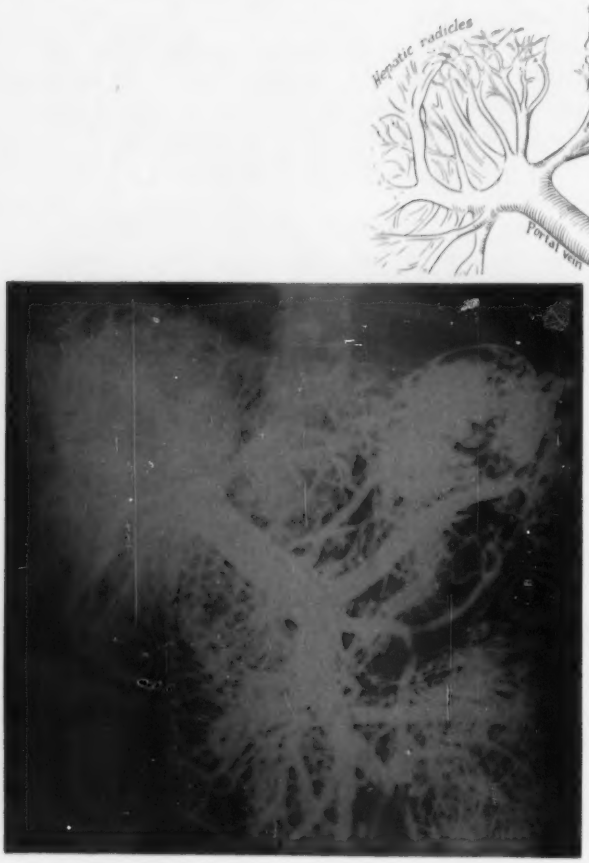

Fig. 1. Postmortem portagram: Normal portal system. Note the almost cylindrical shape of the portal vein. The coronary vein drains into the portal vein, the inferior mesenteric vein into the superior mesenteric vein.

for example, the portal vein is usually easily recognized. It is a vessel, generally straight in its course, which may be tubular or slightly tapering in outline. It may be necessary, however, to distinguish between the portal vein and a large bridging collateral vein which, for example, may occur in agenesis (aplasia) of the portal vein. The collateral in this situation is more likely to be a curved structure and there may even be multiple veins bridging the defect. The splenic vein must also be readily identified. Confusion with the coronary vein, which as our experience indicates is a definite possibility, must be avoided. Figure 1 shows a normal postmortem portagram. In this study filling of practically all of the tributaries of the portal venous system has occurred. Since there is no blood flow to influence filling of the vessels, all the vessels fill centrifugally from the site of injection. The portal vein is normally the largest vein of the portal system, the superior mesenteric vein is next in size, and the splenic vein is somewhat smaller than the superior mesenteric. Both are large tributaries of the portal vein. The coronary vein and inferior mesenteric vein, representing somewhat smaller tributaries, show a variation which is quite constant. The coronary vein thus may enter portal vein or splenic vein or the crotch between the two. The inferior mesenteric vein may drain into the superior mesenteric vein or the splenic vein or the crotch between the two. Further details of the roentgen anatomy of the portal system are considered in another paper.[3]

In the normal portagram in the living, we see only those vessels which lie in the path of the blood flow to the liver. Thus in the normal splenic portagram (Fig. 2*A*) only the splenic vein and the portal vein are opacified. In the normal portal portagram only the vessel injected (here the superior mesenteric vein) and the portal vein are visualized (Fig. 2*B*). This is explainable on the basis of the hepatopetal type of blood flow present in the normal. The visualization of veins (regular or collateral) not in the course of blood flow to the liver is an indication of portal obstruction (allowing a minimum of reflux filling), and generally means a pathologic hepatofugal type of blood flow (reversal of portal blood flow).

Pathologic Anatomy

Basically the portagram reveals anatomic information. Existence or nonexistence of veins can be readily determined if these vessels are in the path of the blood flow. Thus thrombosis may prevent filling of the portal vein. Or the portal vein may be nonexistent due to agenesis

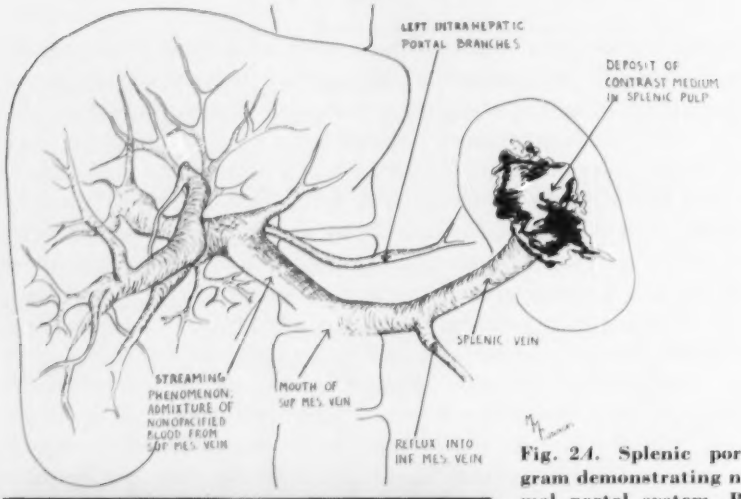

Fig. 2A. Splenic portagram demonstrating normal portal system. Percutaneous injection made directly into spleen. Note the radiolucent band or shading throughout the inferior aspect of the portal vein. This represents stream of nonopacified blood from the superior mesenteric vein (streaming phenomenon). Note also reflux into the inferior mesenteric vein. Reflux of limited extent is considered normal and explained by local transient pressure changes.

Fig. 2B. Portal portagram injected at surgery, demonstrating normal portal system. Only the direct blood stream to the liver is opacified. Note streaming phenomenon caused by nonopacified blood from splenic vein.

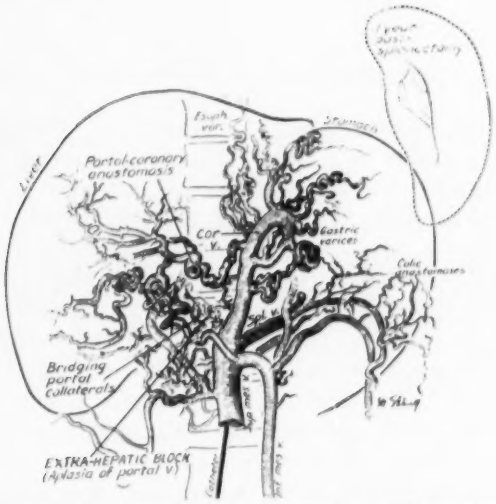

Fig. 3*A*. Drawing illustrating agenesis of portal vein. Note absence of portal vein which produces extrahepatic obstruction. Bridging collaterals carry portal blood from the superior mesenteric and coronary veins to the liver. Extensive gastroesophageal varices are present and splenocolic collaterals arise from the stump of the splenic vein after splenectomy 1 year before. This study performed by injection of cannulized superior mesenteric vein at surgery.

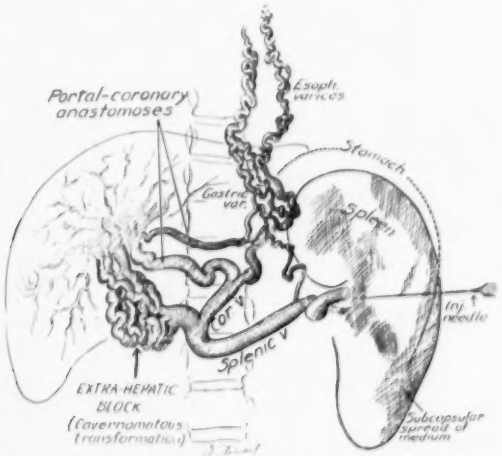

Fig. 3*B*. Drawing illustrating cavernomatous transformation of the portal vein causing extrahepatic obstruction. Much of the portal blood flow is carried by the 2 transhepatic collaterals communicating between the coronary-gastroesophageal veins and intrahepatic portal branches. It is assumed that blood flow is hepatopetal in the transhepatic collaterals (which represent bridging type) since liver is normal and no intrahepatic obstruction is present. However, these vessels are not the equivalent of the normal portal vein and considerable hepatofugal blood flow exists through other collaterals, such as gastroesophageal veins.

(Fig. 3*A*). Position as well as size can be recorded. The splenic or some other vein may occupy an unusual position or may be unusually large or, on the other hand, unusually small in diameter.

Portagraphy is useful in depicting deformities of the veins. Such deformities may be intrinsic and congenital as, for example, in cavernomatous transformation of the portal vein (Fig. 3*B*), or they may be intrinsic and acquired as, for example with a thrombus (Fig. 4). Bland thrombus is not an infrequent occurrence in cirrhosis of the liver, adding extrahepatic obstruction to intrahepatic obstruction.

Cavernomatous transformation of the portal vein is a congenital malformation which is quite readily demonstrated by portal venography because it is an intrinsic deformity. It appears as a somewhat bulbous racemose structure in the course of the vein. Opaque medium may fill the cavernoma and even continue through vessels on the hepatoproximal side of the lesion. However, evidence of obstruction (see Fig. 3*B*) is unmistakable, with the demonstration of collateral veins.

Venous Thrombosis

Venous thrombosis in the portal vein does not always cause the usual roentgen signs that are seen in the extremities. In venograms of the lower extremity thrombosis, when incomplete, manifests itself as a filling defect in the vein, and when complete as a nonfilling of the vein. Recanalization of a thrombosed vein is not infrequently noted in the lower extremity. Secondary signs of hypervascularization of small vessels when thrombosis is recent, and visualization of incompetent vessels when thrombosis is old, may be seen. In the portal system, although complete obstruction of the vein due to a thrombus has been encountered, apparently more often the thrombosis is incomplete and has been extremely difficult to recognize. One suggested explanation for the apparently high incidence of incomplete thrombosis is that blood flow is more rapid in the portal system. Even in a vein, therefore, in which there may be relative stasis (for example, the portal vein in cirrhosis) blood flow may be still rapid enough to prevent complete thrombosis. The volume of blood coming from large tributaries and the rapidity of blood flow would tend to discourage thrombosis to some extent, it would seem. Moreover, the existence of certain collateral veins would (see "Collateral Veins") encourage blood flow even in the face of obstruction and relative stasis. Thus the transhepatic collateral (Fig. 5) would serve as an escape channel for blood in the

Portal Venography

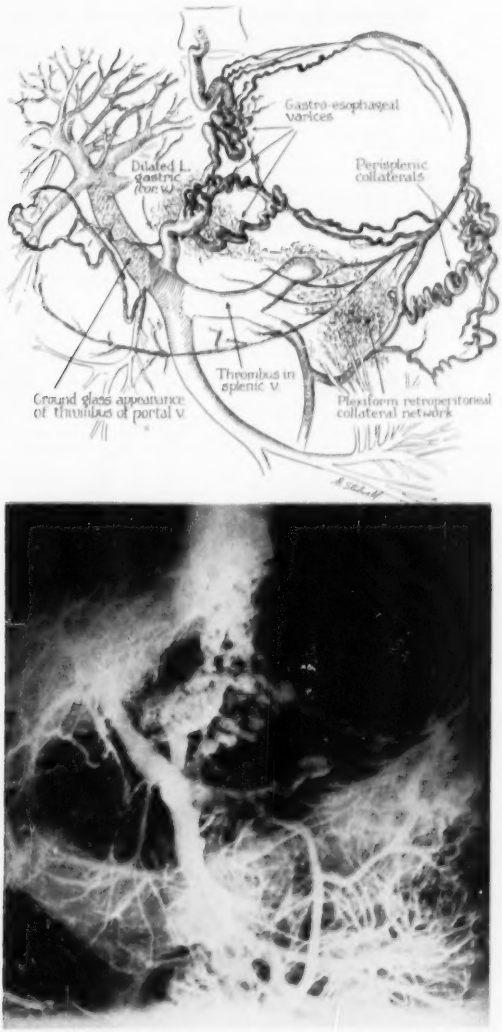
Gastro-esophageal varices
Dilated L. gastric (vein of)
Perisplenic collaterals
Thrombus in splenic v.
Ground glass appearance of thrombus of portal v.
Plexiform retroperitoneal collateral network

Fig. 4. Postmortem portagram in case of liver cirrhosis with bleeding esophageal varices. Note filling defects in splenic vein caused by thrombus. Thrombus produces ground-glass appearance in portal vein. At surgery and autopsy the portal vein was almost completely obstructed by a thrombus which, however, was attached to only one side of vein wall, thus permitting medium to spread about it. Incomplete thrombosis is extremely difficult to recognize in both the living and in the postmortem portagram. Streaming phenomenon might produce similar appearance.

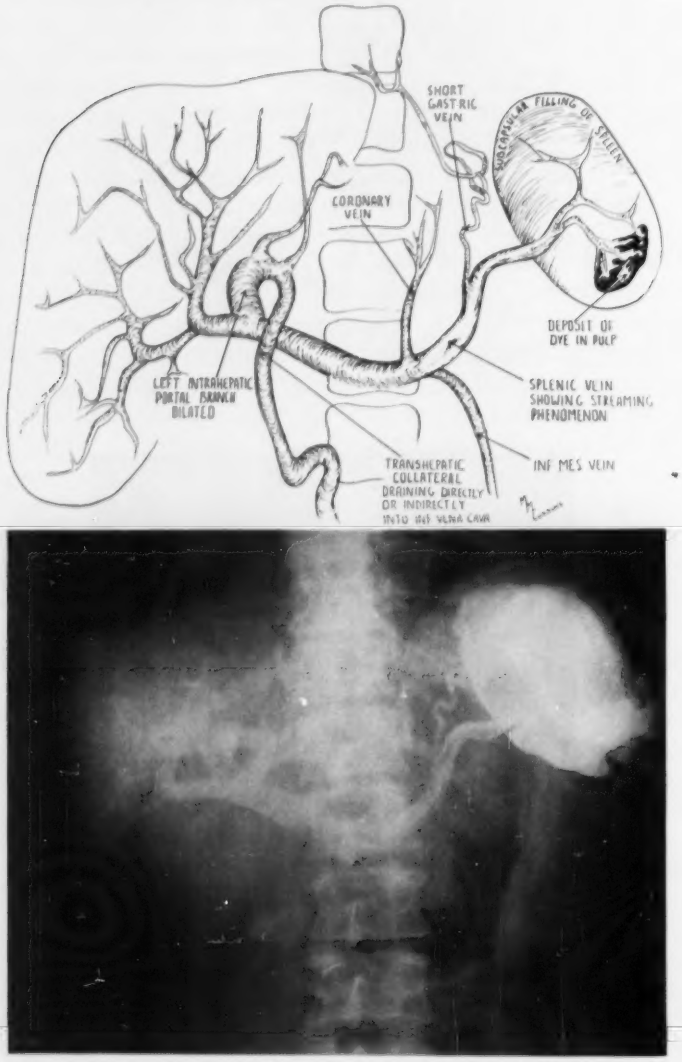
SHORT GASTRIC VEIN
SUBCAPSULAR FILLING OF SPLEEN
CORONARY VEIN
DEPOSIT OF DYE IN PULP
LEFT INTRAHEPATIC PORTAL BRANCH DILATED
SPLENIC VEIN SHOWING STREAMING PHENOMENON
INF MES VEIN
TRANSHEPATIC COLLATERAL DRAINING DIRECTLY OR INDIRECTLY INTO THE VENA CAVA

Fig. 5. Preoperative splenic portagram in case of liver cirrhosis. Note medium-sized transhepatic collateral arising from left intrahepatic-portal branch. Blood flow is hepatofugal toward the inferior vena cava because of intrahepatic obstruction. Note the abnormally widened diameter of the left portal branch. Also note fading phenomenon in splenic and portal veins due to streaming.

portal vein in cirrhosis and thus promote blood flow. Incomplete thrombosis (see Fig. 4) is difficult to visualize radiographically. It may present a ground-glass appearance without definite defect or may produce an actual defect in the vein. Both may be simulated by streaming (see "Factors in Visualization").

Deformities of veins due to extrinsic causes such as abdominal masses also occur. Thus, for example, tumor or cysts of the pancreas may obstruct, narrow, and displace the portal or splenic vein (Fig. 6).

Site of Obstruction

The site of obstruction in the portal system is of considerable importance. The well-established division of portal obstruction into intrahepatic and extrahepatic types may be used to advantage in an understanding of the roentgen findings. The site of obstruction is often quite well determined by the portal venogram. Extrahepatic obstructions are known by the location of the obstruction involving one of the veins. This may be intrinsic as in a thrombus or extrinsic as, for example, splenic artery aneurysm obstructing the splenic vein. Similarly a tumor or cyst of one type or another may reveal its position by extrinsic pressure effect on one of the veins. Intrahepatic obstruction (see Fig. 5) shows no intrinsic or extrinsic deformity of the veins but rather filling of the major veins (splenic and portal) as well as collateral veins. At times an abnormal pattern of the portal vein in the liver may be seen. Diminished arborization of the portal tree and some tendency to distortion of smaller intrahepatic branches has been noted in cirrhosis. Further study of this matter is in progress.

Collateral Veins

One of the most significant and informative findings in the portal venogram in the presence of portal obstruction is the demonstration of collateral veins. Indeed, the presence of collateral veins is a definite indication of portal obstruction. It also suggests the possibility of portal hypertension but in some cases the "compensatory" collaterals may be sufficient to relieve the hypertension. The development of collateral vessels is well recognized as the attempt of the body to bypass a block in a particular portion of the vascular system. These vessels are found in both arterial and venous systems in all portions of the body. At times such collaterals form fairly satisfactory substitutes, although they practically never approach the original vessels in efficiency. Often, however, they are inadequate to a considerable extent and in this set-

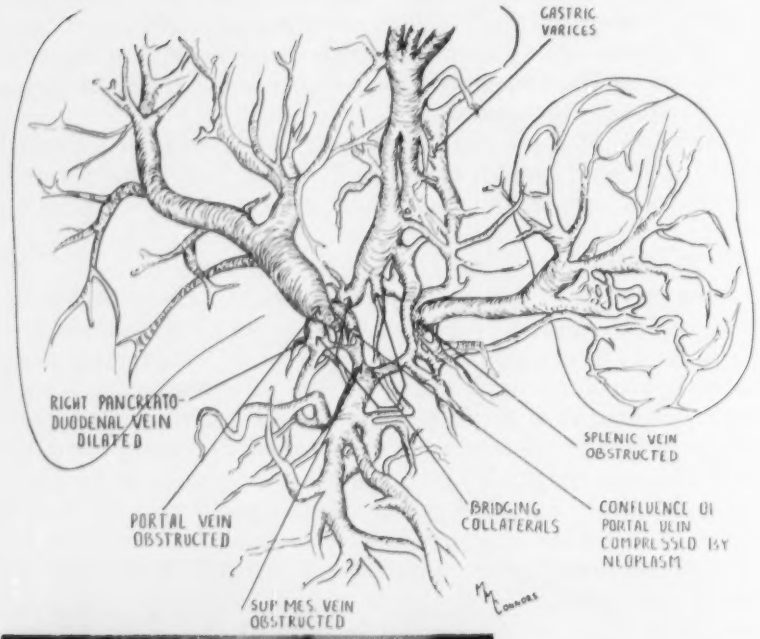

Fig. 6. Extrahepatic obstruction due to carcinoma of pancreas. Obstruction is at the confluence of the major portal tributaries. Note funnel-shaped stenosis of portal vein and occlusion of splenic vein. Bridging collaterals are present in gastrohepatic ligament (postmortem portagram).

ting may produce secondary undesirable effects as, for example, stasis ulcer in the lower extremity and bleeding gastroesophageal varices in portal hypertension. In the portal system, collateral-vein development may be considered to be of two major types: (1) the detour type, by far the most common, which carries blood to the systemic system via a circuitous route, and (2) the bridging type of collateral, in which a vein or veins extend immediately across or close to the obstruction or defect of a particular vein.

During our study of the portal system by venography in both the living and postmortem cases,[4, 7] we have discovered many collateral veins and vein systems. There is some difference in the incidence of the various collaterals in the clinical material (which is entirely surgical) and the postmortem material (which is practically entirely medical). The postmortem portagram, because of the centrifugal type of flow of opaque medium from the site of injection, visualizes almost all vessels of the portal system, including essentially all existing collaterals larger than capillary size. In portagrams made in vivo it is probable that some of the collaterals that exist in a given case are not visualized for technical as well as physiologic reasons. We have seen, therefore, a larger number of different collaterals in the postmortem study than in the examinations made in the living. Nevertheless many of the collaterals have been seen in both and it is with these that we shall be chiefly concerned here. (A comparison of the surgical and postmortem material and the significance of the difference encountered is discussed elsewhere.[4, 7]) It should be stated that the number of possible collateral veins and vein systems appears to be great and it is quite probable that additional collaterals not yet identified will be found.

Coronary Esophageal Collateral. In the portagrams made in the living (selected since these were cases of portal hypertension with gastroesophageal bleeding referred for surgical treatment) the coronary gastroesophageal collateral was almost invariably present (Fig. 7). This of course was expected since this is precisely the cause of the patient's difficulty. It is interesting to note that in all cases tortuous gastric veins were seen along the lesser curvature. Whether all of these represented bleeding varices is an undetermined question. Nevertheless, dilated gastric veins were seen in all the cases, whereas in only about two thirds to three quarters of the material were esophageal varices demonstrated by venography. A possible explanation for failure of development of esophageal varices in the presence of dilated gastric veins is that the

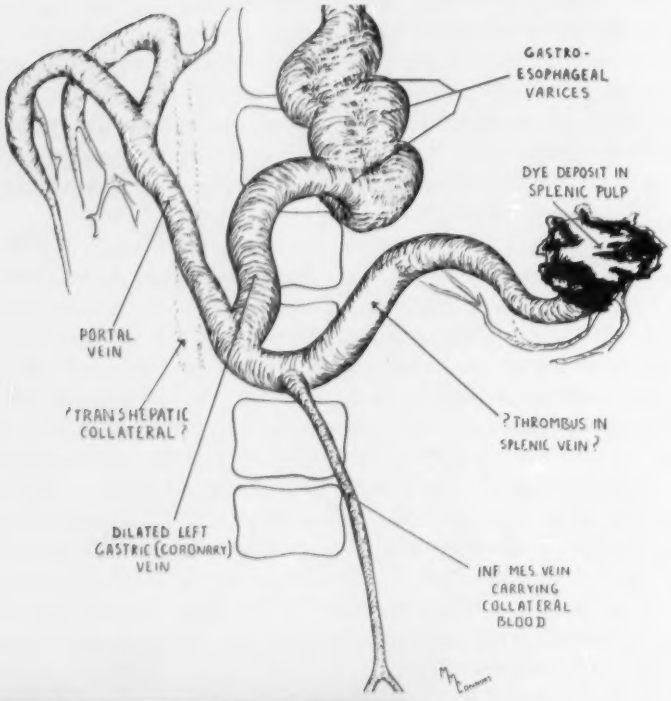

Fig. 7. Preoperative splenic portagram. Liver cirrhosis with bleeding esophageal varices. Note hugely dilated coronary (left gastric) vein and gastroesophageal varices. Filling of inferior mesenteric vein indicates pathologic hepatofugal blood flow.

blood was shunted to retroperitoneal veins directly from the gastric veins (suggested from the postmortem study).

Transhepatic Collateral. A second collateral of surprisingly high incidence is the transhepatic collateral (see Figs. 3*B* and 5). This vessel, found in both postmortem and intra-vitam studies, arises in the liver, more often from the left but occasionally from the right main branch of the portal vein. At times it is quite large and extends to join various systems. Thus it may join the coronary vein but more often extends posteriorly toward a retroperitoneal plexus. We believe that at times it communicates with the adrenal-renal veins. It may even occasionally empty directly into the cava. Occasionally it will communicate with the vertebral plexus, and may join veins on the right side or extend completely across to the left side of the body. The transhepatic collateral occurred in more than one half of our venograms made in the living and was the second most frequently encountered collateral.

Collateral Arising from the Splenic Vein. This extended to the retroperitoneal plexus of veins and was the third most common collateral. Probably in some of these cases communication was made with the adrenal-renal veins. This collateral was seen in about one third of our cases.

Other Collaterals. In about a fourth of the cases each of the following natural shunts was seen: superior mesenteric vein to retroperitoneal veins, inferior mesenteric vein to hypogastric vein, and multiple veins arising from the coronary and its gastric tributaries and extending to the retroperitoneal plexus. Retroperitoneal communications with various portal tributaries were quite frequent, some form being present in about two thirds of the cases. In about one third of the total cases examined there was evidence of communication of the portal system with the hypogastric vein. Usually this occurs via the inferior mesenteric vein but occasionally via a long vein arising from the spleen or splenic vein.

PHYSIOLOGIC IMPLICATIONS OF PORTAGRAPHIC FINDINGS

Most of the deductions concerning the physiology, both normal and abnormal, that are made are indirect and arrived at by an analysis of certain anatomic findings in correlation with known clinical facts. We can thus for example determine that blood flow in a particular portagram is hepatofugal when we know: (1) that the normal direction of portal blood flow is hepatopetal; (2) that in the normal portagram only

those vessels lying along a direct course to the liver from site of injection to liver would be visualized; and (3) that if any vessel other than these is demonstrated, such vessel or vessels are playing a part in carrying blood around a block and are therefore acting as collateral vessels

Site of Obstruction

The site of obstruction is of vital importance for consideration in an attempt at evaluation of the physiologic implications of the portagram. It not only gives definitive anatomic information as, for example, thrombosis, but taken with other known clinical facts will often indicate the direction of blood flow. Thus, in the example of cavernomatous transformation of the portal vein referred to before, in which a normal liver is established on clinical grounds, it is proper to assume that a transhepatic collateral extending from the coronary to the left main branch of the portal vein is carrying blood hepatopetally rather than hepatofugally, since there is no obstruction in the liver. On the contrary, in cirrhosis of the liver with intrahepatic block it is probable that the blood would travel hepatofugally through such a transhepatic collateral.

Increase in Vessel Size

An increase in vessel size may be used as a sign of portal obstruction and, when evaluated with certain other factors, may suggest the direction of blood flow. The amount of blood flow through a vessel appears to be a significant determinant of vessel size. Thus, for example, a vein may be dilated over its entire length if the entire vein is functioning as a collateral, or only a segment may be enlarged when that part alone is serving as part of the collateral route. Thus, for example, as seen in Fig. 8, the portal vein is considerably dilated up to the point where the coronary takes over, carrying blood away from the portal vein in a hepatofugal direction. That part of the portal vein above the coronary and closer to the liver has become relatively smaller in diameter. Varying degrees of stasis may account to some extent for vessel size, and thus increased volume of blood may be a more satisfactory explanation for vessel size than amount of blood flow per unit of time. In either event the vessel contains more blood than normal and apparently enlarges to accommodate this increased amount of blood.

Size and Source of Collaterals

The relative importance of various collaterals can be determined to some extent by the size of these collaterals as well as the size of the major tributaries of the portal system which feed them. Thus a large

Portal Venography

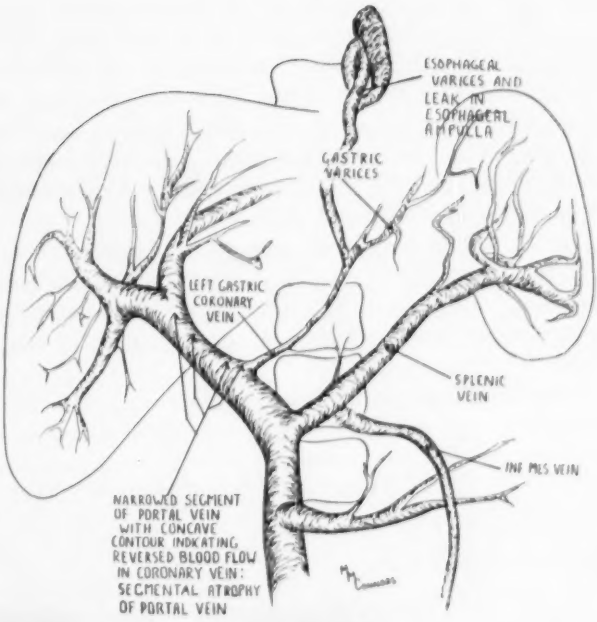
ESOPHAGEAL VARICES AND LEAK IN ESOPHAGEAL AMPULLA
GASTRIC VARICES
LEFT GASTRIC CORONARY VEIN
SPLENIC VEIN
INF MES VEIN
NARROWED SEGMENT OF PORTAL VEIN WITH CONCAVE CONTOUR INDICATING REVERSED BLOOD FLOW IN CORONARY VEIN: SEGMENTAL ATROPHY OF PORTAL VEIN

Fig. 8. Postmortem portagram in case of liver cirrhosis with intrahepatic obstruction. Note the decrease in diameter of the hepatoproximal two thirds of portal vein due to atrophy. Blood has been shunted through the coronary vein, not yet dilated to gastric and esophageal varices demonstrated at autopsy, but barely suggested on this film.

splenic vein with a large collateral arising from the splenic vein and extending down toward the hypogastric vein may, by virtue of its being the largest collateral demonstrable, indicate that it is the most important natural shunt that has developed in a particular case of portal hypertension. The most important collaterals in each case are usually visualized in a portagram, since the opaque material is swept along in the direction that most of the blood is traveling. At times, nevertheless, owing to various technical as well as physiologic features, it is possible that in a given instance all of the important collaterals may not be visualized. Possibly serial filming will reveal further information by sequential filling of collaterals and thus afford a means of direct observation as against indirect deduction for evaluation of some of the features that have been discussed.

Most of the time blood flow through a collateral is in a hepatofugal direction and only occasionally is it in a hepatopetal direction. Hepatopetal blood flow would be very unlikely to occur in the presence of an intrahepatic obstruction. However, as we have seen, it may occur in extrahepatic obstruction.

Factors in Visualization

There are several factors which apparently influence demonstration of collateral veins and vein systems by injected opaque medium. Perhaps the most important is the size of the vessel, since increased size usually means increased volume of blood and often increased blood flow. One would assume that the opaque material would be swept along in the direction that most of the blood is moving. Another factor of considerable importance is the site of injection. Those vessels closest to the site of injection tend to fill first, providing, of course blood is flowing in that particular direction. It is conceivable, however, that a smaller collateral closer to the site of injection would be visualized *after* a larger collateral at a greater distance from the site of injection. Eventually all important collaterals carrying blood should fill. But a single-exposure technic may not reveal all such collateral veins filled.

The streaming phenomenon is still another force which probably influences visualization of various collaterals to some extent. This may occur when blood from tributaries pouring into a particular vein does not immediately mix with blood in that vein, but rather continues in a separate stream or streams for a variable distance. This obviously would produce radiolucent streaking in the opaque column of blood (Fig. 9). It is conceivable that a radiopaque medium injected into a vein that is producing such a stream may not immediately visualize an impor-

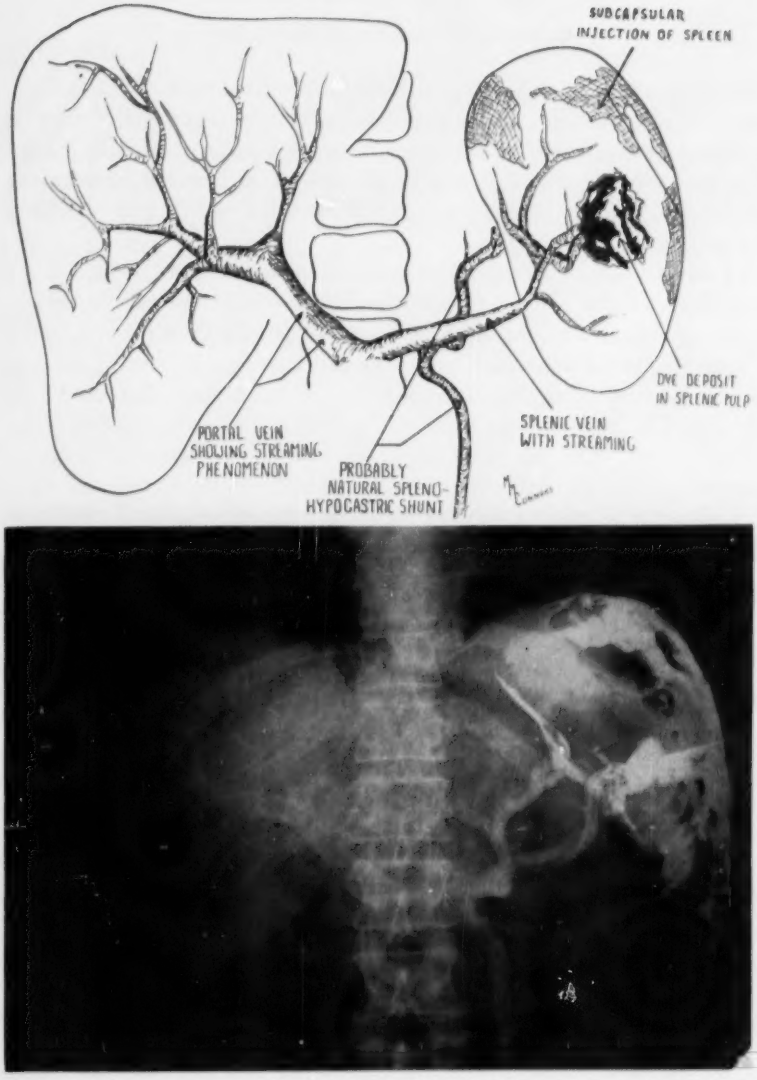

Fig. 9. Splenic portagram. Liver cirrhosis with bleeding gastroesophageal varices. Note extensive streaming phenomenon throughout splenic and portal veins. There is a collateral vessel arising from the spleen, crossing the splenic vein, and extending inferiorly to the left of the spine. Its further communications are not determined. Its position suggests possible anastomosis with the hemorrhoidal plexus. Partial subcapsular injection of contrast medium in spleen occurred.

tant collateral that was not in the direction of the flow. For example, injection of a superior mesenteric vein in such a case might result in nonfilling of an inferior mesenteric vein that arose from the splenic vein and which was not in the direct stream of blood flow from the superior mesenteric vein. Reflux filling, however, might later visualize the inferior mesenteric vein.

In our experience we have noted two types of change caused by streaming. One is a fading phenomenon, in which one portion of the vein (see Fig. 4) is of homogeneous but less density than the remainder of the opaque column. Such a shaded appearance may readily be confused with the ground-glass appearance of thrombus described previously. The second type produces a defect suggestive of an intraluminal mass. This defect may even have a somewhat lobulated appearance and may also be extremely difficult to differentiate from a thrombus. At times an area of radiolucency appears in an opacified vein at the mouth of the tributary. This is readily recognized as a jet of nonopacified blood entering the vein.

SUMMARY

Portal venography has come of age. The various useful anatomic and physiologic data which may be derived from the portal venogram include:

The existence or nonexistence of vessels of the portal system, and their position, size, and relationships. This can be important and even vital information to the surgeon contemplating vascular surgery.

Demonstration of varices and other intrinsic lesions of the veins. The anatomic extent of these abnormal blood vessels is revealed.

Information concerning lesions producing deformities of the veins that may displace or deform or obstruct the whole or a segment of the portal venous system. The portagram will thus help to determine whether an intra- or extrahepatic type of obstruction exists.

Demonstration of collaterals or shunts that the body has developed in an attempt to combat portal obstruction. The portal venogram thus affords evidence of portal obstruction and suggests the possibility of portal hypertension. It furthermore presents the opportunity of deliberate thought concerning the question of sacrifice or preservation of a particular collateral vein or vein system in surgical planning.

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Hyperchlorhydria Induced by Intravenous Reserpine

Response to Various Therapeutic Agents

EDWARD M. SCHNEIDER, M.D., and MERVIN L. CLARK, M.D.

Rauwolfia serpentina and its various alkaloids have become popular therapeutic agents in American medicine. The tranquilizing properties attributed to them,[9, 11, 12] associated with what some workers assume to be more specific hypotensive effects,[1, 11, 14, 16] provide most of the impetus for this popularity.

Nevertheless, the site or sites wherein the various alkaloids of *Rauwolfia* exert their apparent salutory effects have eluded studies to date. Most workers believe that their primary influence is central—probably in the hypothalamus.[1, 3, 4, 10, 11, 17]

The undesirable side effects of *Rauwolfia* and its various alkaloids include psychic aberrations, most notably nightmares and depression, nasal stuffiness, abdominal cramps, and diarrhea.[1, 7, 10, 11, 15–17] The latter side effects are regarded by many as evidences of either parasympathomimetic or sympatholytic activity. Some confirmation of the existence of one or the other of those possibilities was presented in the work of Plummer *et al.* They demonstrated gastrointestinal hypermotility and gastric hyperacidity in dogs following parenteral administration of reserpine. They further showed that an anticholinergic compound (oxyphenonium bromide) would effectively block this response. In addition, Barrett *et al.*[2] have demonstrated that reserpine induced hyperchlorhydria in the vagally denervated dog stomach (Heidenhain pouch). This suggests a peripheral site of reserpine activity.

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Published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

The present study was undertaken on the assumption that much can be learned about the primary action of a drug by studying its so-called side-effects.

METHODS

In a previous study[6] 24 subjects received 1 mg. of reserpine intravenously. This produced a sustained hyperchlorhydria, with onset at about 30 minutes. This hyperchlorhydria was significant when compared to the responses of 11 of these same subjects following an intravenous injection of saline (Fig. 1). Confirmation of this effect of

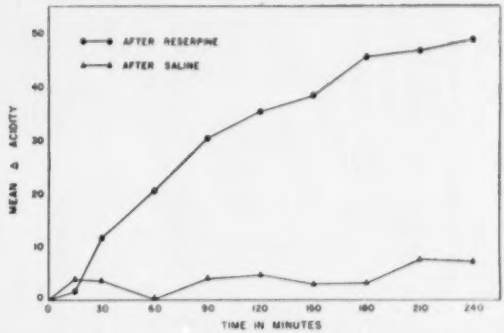

Fig. 1. Mean change in free hydrochloric acid (Δ acidity) for each collection period for both reserpine and saline control groups.

intravenous administration of reserpine in man has recently been presented by others.[5, 6]

In attempt to evaluate the mechanism of this response, a series of three different drugs whose specific modes and sites of action are supposedly known were given simultaneously with reserpine to three separate groups of 10 subjects each. These subjects were studied using the basic methods previously reported.[6]

Dosage

With 1 mg. of reserpine* intravenously:

Group 1 received 0.3 mg. of atropine sulfate intravenously.

Group 2 received 50 mg. of methantheline bromide (Banthine) intravenously.

Group 3 received 0.4 cc. of 1:1000 epinephrine subcutaneously.

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* Medication provided by E. R. Squibb and Sons—2 cc. ampules reserpine solution for injection, 2.5 mg. per cc.

TABLE 1. Effect of Atropine on Reserpine-Induced Hyperchlorhydria

Subject	Max. base acid[a]	15 min.		30 min.		60 min.		90 min.		120 min.		150 min.		180 min.		210 min.		240 min.	
		′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ
1	0	0	0	20	20	35	35	55	55	80	80	55	55	65	65	60	60	70	70
2	50	35	−15	45	−5	55	5	70	20	60	10	75	25	65	15	80	30	90	40
3	0	0	0	0	0	0	0	0	0	0	0	5	5	10	10	25	25	30	30
4	40	10	−30	5	−35	50	10	60	20	60	20	90	50	80	40	90	50	100	60
5	45	25	−20	60	15	110	65	100	55	100	55	90	45	100	55	105	60	100	55
6	10	10	0	40	30	65	55	70	60	80	70	85	75	80	70	85	75	90	80
7	0	0	0	0	0	0	0	0	0	25	25	60	60	55	55	40	40	85	85
8	35	10	−25	15	−20	75	40	75	40	100	65	100	65	85	50	100	65	105	70
9	40	40	0	40	0	55	15	65	25	80	40	20	−20	70	30	35	−5	70	30
10	35	50	15	60	25	30	−5	40	5	60	25	55	20	70	35	70	35	80	45
Mean	25.5	18	−7.5	28.5	3	47.5	22	53.5	28	64.5	39	63.5	38	68	42.5	69	43.5	82	56.5
S.D.	20.5	18.3	14.2	23.5	20.3	33.4	25	32.1	23.3	31.7	27.3	31.3	29.9	24	20.2	28.1	23.6	21.9	19.9

[a] Highest of three determinations of free acid during the hour before administration of medications (c.u.[mEq./L.]).
′ Acidity at given time following medications (c.u.[mEq./L.]).
Δ Difference between maximum baseline acidity and acidity at given time following medications.

The period of observation in each instance was 5 hours, including a 1-hour control period before medication. The highest value of free gastric acid during the control period was used as a basis for further comparison and is expressed in clinical units (mEq./L.). The change in acidity following medication for each time period is indicated by the symbol Δ. All data were statistically analyzed.

EFFECTS ON ACIDITY

Atropine

Table 1 summarizes the data obtained on 10 patients who received atropine 0.3 mg. along with reserpine.

The mean change in acidity of the group at various time intervals during a 240-minute observation period is graphically recorded in

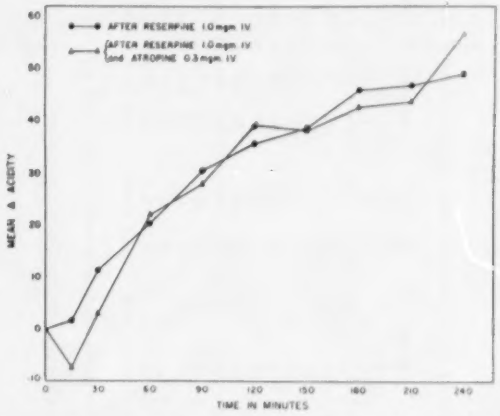

Fig. 2. Comparison of mean change in free hydrochloric acid (Δ acidity) in patients receiving reserpine plus atropine and patients receiving reserpine alone.

Fig. 2. No significant effect on reserpine-induced hyperchlorhydria could be detected. In fact, the similarity of the curves obtained using atropine plus reserpine and reserpine alone is striking.

Methantheline Bromide

In Table 2 the data obtained in the study of 10 patients who received methantheline bromide (Banthine) 50 mg. intravenously plus reserpine are recorded. When compared with the group which received reserpine alone, a significant suppression of gastric acidity could be demonstrated at 15 ($p = .001$) and 30 ($p = .01$) minutes,

TABLE 2. Effect of Banthine on Reserpine-Induced Hyperchlorhydria

Subject	Max. base acid[a]	15 min.		30 min.		60 min.		90 min.		120 min.		150 min.		180 min.		210 min.		240 min.	
		′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ
1	30	20	−10	20	−10	20	−10	25	−5	30	0	30	0	40	10	65	35	30	0
2	40	30	−10	40	0	60	20	40	0	40	0	45	25	70	30	70	30	85	45
3	15	0	−15	0	−15	80	65	90	75	100	85	90	75	70	55	65	50	60	45
4	30	35	5	35	5	70	40	80	50	90	60	95	65	100	70	95	65	90	60
5	45	35	−10	30	−15	30	−10	50	5	50	5	55	10	60	15	50	5	45	0
6	15	0	−15	0	−15	15	0	45	30	55	40	60	45	75	60	65	50	50	35
7	30	30	0	40	10	40	10	55	25	50	20	60	30	55	25	65	35	60	30
8	30	20	−10	20	−10	30	0	50	20	60	30	55	25	60	30	50	20	65	35
9	25	25	0	25	0	35	10	40	15	50	25	65	40	60	35	60	35	75	50
10	10	10	0	10	0	25	15	55	45	80	70	90	80	75	65	70	60	85	75
Mean	27	20.5	−6.5	22	−5	41	14	53	26	60.5	33.5	66.5	39.5	66.5	39.5	65.5	38.5	64.5	37.5
S.D.	11.1	13.2	7.1	14.9	9.1	21.8	23.3	19.2	24.0	22.4	29.9	20	27	15.8	21.4	12.6	18.3	19.5	23.7

[a] Highest of three determinations of free acid during the hour before administration of medications (c.u.[mEq./L.]).

′ Acidity at given time following medications (c.u.[mEq./L.]).

Δ Difference between maximum baseline acidity and acidity at given time following medications.

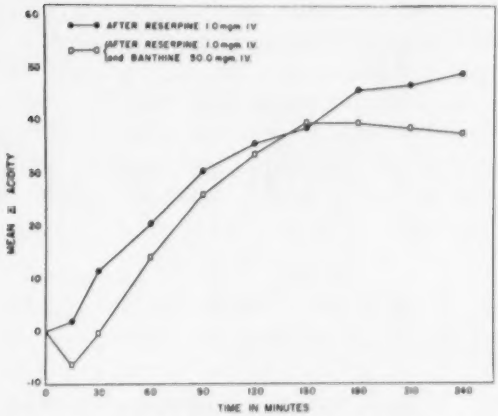

Fig. 3. Comparison of mean change in free hydrochloric acid (Δ acidity) in patients receiving reserpine plus Banthine and patients receiving reserpine alone.

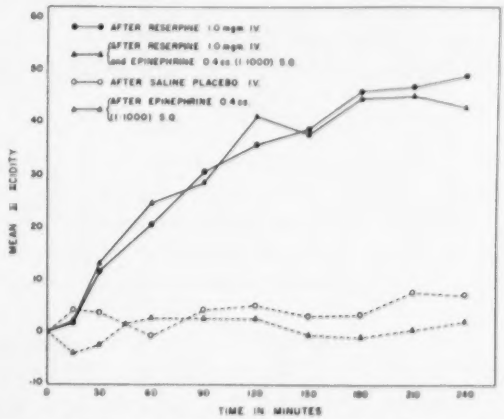
AFTER RESERPINE 1.0 mgm. I.V.
AFTER RESERPINE 1.0 mgm. I.V. and EPINEPHRINE 0.4 cc. (1:1000) S.Q.
AFTER SALINE PLACEBO I.V.
AFTER EPINEPHRINE 0.4 cc. (1:1000) S.Q.
MEAN Δ ACIDITY
TIME IN MINUTES

Fig. 4. Comparison of mean free hydrochloric acid (Δ acidity) in patients receiving epinephrine plus reserpine and patients receiving reserpine, epinephrine, or saline alone.

but not thereafter. The result of this study is recorded in Fig. 3. Once again the similarity of the pattern of response of the test group to that of the group who received reserpine alone is apparent.

Epinephrine

The effect of epinephrine 0.4 cc. 1:1000 subcutaneously and reserpine 1 mg. intravenously is recorded in Table 3 and is shown

TABLE 3. Effect of Epinephrine on Reserpine-Induced Hyperchlorhydria

Subject	Max. base acid[a]	15 min.		30 min.		60 min.		90 min.		120 min.		150 min.		180 min.		210 min.		240 min.	
		′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ	′	Δ
1	10	10	0	15	5	20	10	20	10	40	30	35	25	55	45	50	40	50	40
2	55	55	0	85	30	90	35	85	30	95	40	95	40	95	40	95	40	80	25
3	30	35	5	35	5	50	20	75	45	90	60	90	60	100	70	95	65	105	75
4	60	55	−5	55	−5	50	−10	50	−10	65	5	50	−10	65	5	35	−25	50	−10
5	45	40	−5	50	5	50	25	95	50	100	55	110	65	100	55	105	60	115	70
6	30	50	20	65	35	85	55	80	50	95	65	95	65	90	60	110	80	90	60
7	30	25	−5	50	20	75	45	75	45	80	50	95	65	80	50	85	55	75	45
8	0	0	0	0	0	20	20	30	30	45	45	35	35	40	40	55	55	35	35
9	25	25	0	10	−15	20	−5	20	−5	30	5	5	−20	—	—	—	—	—	—
10	25	35	10	75	50	75	50	65	40	75	50	75	50	60	35	60	35	70	45
Mean	31	33	2	44	13	56	24.5	59.5	28.5	71.5	40.5	68.5	37.5	76.1	44.4	76.6	45	74.4	42.8
S.D.	18.5	18.4	7.9	28.5	20.2	28.4	22.2	27.7	22.5	25.4	21.2	34.8	31	21.9	18.4	27	29.8	26.5	25.6

[a] Highest of three determinations of free acid during the hour before administration of medications (c.u.[mEq./L.]).
′ Acidity at given time following medications (c.u.[mEq./L.]).
Δ Difference between maximum baseline acidity and acidity at given time following medications.

graphically in Fig. 4. There is no significant effect exerted by epinephrine on reserpine-induced hyperchlorhydria. In order more fully to evaluate the effect of epinephrine on gastric secretion, an additional 10 subjects were studied following subcutaneous administration of 0.4 cc. of 1:1000 epinephrine alone. A comparison of the response obtained with that obtained in 11 other subjects who received saline intravenously is also recorded in Fig. 4. No significant difference was demonstrated.

DISCUSSION

Atropine and epinephrine in therapeutic doses do not exert any effect on reserpine-induced hyperchlorhydria. Banthine produces a fall in gastric acidity at 15 and 30 minutes. However, this response might well reflect only a blocking of normal gastric secretory mechanisms, since reserpine does not usually induce hyperchlorhydria in less than 30 minutes after injection. Although these data are inconclusive, they suggest that the reserpine effect on gastric acidity may be mediated by a humoral, or peripheral, rather than a central neurogenic mechanism. Further studies are necessary.

SUMMARY AND CONCLUSIONS

In a previous study, a fairly rapid, prolonged, and significant hyperchlorhydria was demonstrated in patients following the intravenous injection of 1 mg. of reserpine. The present study was designed to test the response of this reserpine effect to atropine 0.3 mg. intravenously, Banthine 50 mg. intravenously, and epinephrine 0.4 cc. 1:1000 subcutaneously.

The therapeutic agents used had no significant effect upon reserpine-induced hyperchlorhydria. The results of this study suggest that the reserpine effect on gastric acidity is most probably a humoral, or peripheral, type of response rather than a central neurogenic effect.

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Prantal in Long-Term Anticholinergic Therapy

JACOB A. RIESE, M.D.

SINCE a recent comparison[11] of the effectiveness of several anticholinergic agents, efforts to find the ideal agent have continued. In the search, interesting work by Shay[12] and Shay and Sun[13] on the relation of stress to gastric secretion and peptic ulcer has been noted as well as demonstrations of the effects of drugs of this class on gastric secretion and motility.[3, 5-8]

PREVIOUS EXPERIENCE WITH ANTICHOLINERGIC DRUGS

The ideal anticholinergic drug would be one capable of relieving pain without causing side reactions. The stimulus for an evaluation in these respects of propantheline bromide,[2, 10, 14] methscopolamine bromide,[5, 7] and diphemanil methylsulfate[4, 9, 15] came from experience in the use of these substances* in 3 private patients. The patients were referred by their physicians because of severe upper abdominal pain resulting from duodenal ulcer. Therapy with propantheline bromide had had to be abandoned because of dryness of the mouth and blurring of vision to an intolerable degree.

When these patients were first seen, 2 100-mg. diphemanil methylsulfate tablets every 4 hours were prescribed. This therapy completely relieved the pain within 2 weeks, and there were no side effects. After pain was relieved a dosage of 1 tablet every 6 hours was continued for 1 month. The medication was then changed to 1 100-mg. diphemanil methylsulfate repeat-action tablet twice daily, or 1 tablet, 100 mg. with phenobarbital ¼ gr., 3 times daily. One or the other of these forms was continuously administered to these 3 patients for 3 months with no side effects.

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* Propantheline bromide was used as Pro-Banthine (Searle & Co., Chicago, Ill.); methscopolamine bromide was used as Pamine (The Upjohn Co., Kalamazoo, Mich.); and diphemanil methylsulfate was used as Prantal (Schering Corporation, Bloomfield, N. J.).

COMPARATIVE STUDY

Subjects

Twenty-six patients with gastric or duodenal ulcer—14 from the Gastrointestinal Clinic and 12 private patients—were selected for a comparative study of the effects of three of the drugs currently used in anticholinergic therapy of peptic ulcer. Twenty-one patients had duodenal ulcers proved by x-ray examination, and 5 had gastric ulcers; these were associated with hypertrophic gastritis in 2. The radiologic findings of gastric ulcers were verified by gastroscopy.

All 26 patients had moderate to severe pain at the start of treatment. Six vomited persistently despite the lack of evidence of pyloric obstruction. The duodenal ulcers in these 6 patients probably were pyloroduodenal, as experience has shown that pyloric ulcers, or duodenal ulcers at the pyloric juncture, may give rise to vomiting.

Therapy and Results

Initially all 26 patients were treated with propantheline bromide in a dosage of 15 mg. 4 times daily. After 2 weeks, 10 patients had to discontinue the drug. While pain was relieved, dryness of the mouth, blurring of vision, and difficulty in urination[2, 8, 10, 14] prevented its continued use. Extreme dryness of the mouth and throat was the predominant complaint. The same side effects occurred to a moderate degree in the remaining 16 patients, but they were able to continue therapy at this level for 1 month.

Pain Relief

Propantheline bromide completely relieved or controlled pain in 20 of the 26 patients. Six patients with incomplete pain relief thought that it aggravated ulcer pain.

Eventually the 26 patients were placed on a dosage of 1 or 2 2.5-mg. methscopolamine bromide tablets every 6 hours. The higher dosage was used for patients with severe ulcer pain, and the lower dosage in patients with moderate pain. Under this therapy pain disappeared in 22 patients and was partially relieved in 2. Two patients reported aggravation of pain. Treatment at both dosage levels was complicated by dryness of the mouth, blurred vision, and difficulty in urination.[1, 2, 5, 7] These side reactions were severe in 2 patients, moderate in 16, and mild in 6. Methscopolamine bromide could be continued for only 2 weeks to 1 month because of them.

The third drug used by all 26 patients in this series was diphemanil

methylsulfate (Prantal). The usual dosage was 1 100-mg. Prantal tablet 4 times daily. In patients with severe pain, a dosage of 200 mg. was used 4 times daily for 1 or 2 weeks, or until the severe pain was relieved. The dosage thereafter was maintained at 100 mg. 4 times daily until freedom from pain was achieved, usually about two months.

Prantal relieved pain completely in 22 patients, partially in 2, and aggravated ulcer pain in 2. No side effects were reported by or elicited upon questioning of 24 patients. Dryness of the mouth occurred in 2 patients, causing discontinuation of therapy in 1. All other patients continued taking Prantal as long as necessary for the relief of complaints.

SUMMARY

The anticholinergic drug diphemanil methylsulfate (Prantal) was highly effective for the relief of pain from gastric and duodenal ulcers. Side effects were infrequent or lacking in its use in dosages up to 800 mg. daily. Prantal was slightly more effective than both propantheline bromide and methscopolamine bromide in relieving pain in these 26 patients, and could be continued at effective dosage levels for longer periods without causing severe side effects. Dryness of the mouth, blurred vision, and difficulty in urination were not encountered in the use of Prantal.

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MEDICAL GRAND ROUNDS

Hirschsprung's Disease

E. Clinton Texter, Jr., M.D., *editor*

Report of a weekly Medical Grand Round held at the VA Research Hospital-Northwestern University Medical Center, Chicago, Ill. Presented by staff members of the VA Research Hospital and participated in jointly by the faculty and clinical clerks of Northwestern University Medical School and guests.

Dr. Craig W. Borden: This morning's conference will be devoted to a discussion of Hirschsprung's disease (aganglionic megacolon). Dr. Holt will present the case.

Dr. Francis J. Holt:

G. K. (#5061-3071), an 18-year-old white male, was admitted to the Research Hospital on June 20, 1955. According to his mother, the patient had been unable to have a bowel movement without the aid of rectal suppositories after the first few days of life. Because of increasing constipation, the patient was taken to Billings Hospital at the age of 2, where an x-ray diagnosis of megacolon was made. The patient used laxatives and enemas frequently, but matured normally. He was inducted into the Navy in 1954. His constipation became progressively more severe with recurring fecal impactions, and after two weeks of obstipation, he entered the Great Lakes Naval Hospital in April 1955. X-rays at that time confirmed the diagnosis of megacolon. Following discharge from the Navy, the patient lived a relatively normal life with the use of three to four enemas weekly and daily laxatives.

Physical examination on admission revealed a well-developed young adult male of asthenic habitus. Blood pressure was 120/80, and the pulse rate was 88. The head and neck were within normal limits. The lungs were clear except for coarse breath sounds over the lower half of the right hemithorax. The heart was not enlarged, the rhythm was regular, and no murmurs were heard. The abdomen was soft and not distended. No masses or

The illustrations were made by Mr. Frederick Hartman of the VA Research Hospital. Dr. Hubbard W. Smith and Miss Junko Ikeya assisted in the preparation of the conference.

Fig. 1. X-ray of colon.

Fig. 2. X-ray of kidney and ureter.

viscera were palpable. Examination of the rectum revealed a normal ampulla and anal sphincter. The genitalia and extremities showed no abnormalities. Proctoscopy revealed a narrowed segment at 12 cm., opening into a cavernous, dilated sigmoid.

Admission hemoglobin was 16.2 Gm./100 cc., with a normal white count and sedimentation rate. Urinalysis showed no microscopic abnormalities, a maximum specific gravity of 1.019, and a phenolsulfonphthalein excretion of 13.5 per cent in 15 minutes. Blood urea nitrogen was 13.2 mg./100 cc. A barium-enema study disclosed typical findings of Hirschsprung's disease, with marked dilatation of the colon, and a narrowed sigmoid segment 3 cm. long which was continuous with the rectum (Fig. 1). Intravenous pyelogram showed a right hydronephrosis, and a retrograde study revealed megaloureter on the same side (Fig. 2). Cultures of the urine obtained from the bladder and from the right kidney were negative. Nonspecific T wave changes in leads II, III, aVL, and V_5 and V_6 were present in the electrocardiogram.

Because of the progression of the patient's symptoms, surgery was advised, and on August 2, 1955, a low anterior resection was performed with removal of the dilated loop and as much of the narrowed distal rectosigmoid area as could be readily accomplished. During surgery, a sinus tachycardia developed, at a rate of 165. This was accompanied by a fall in blood pressure to 80/60, despite adequate transfusion. Hemoglobin done during surgery was 18 Gm./100 cc.

Following surgery, initially the patient did well with the aid of a Miller-

Abbott tube and a rectal tube. However, the tachycardia persisted and on the second postoperative day the temperature rose to 101°F. Despite the persistence of fever, bowel sounds returned on the third day, and stool was passed through the rectal tube. Erythromycin 1.0 Gm./day and tetracycline 1.0 Gm./day were begun intravenously. On the fourth postoperative day, the patient's blood pressure suddenly became unobtainable, and during the next 24-hour period the urine output dropped from 1400 cc. to 150 cc. X-ray study revealed air beneath the diaphragm and no evidence of pneumonitis in the chest. Cultures of the peritoneal fluid and 3 aerobic and anaerobic blood cultures were negative, while a urine culture showed *Bacillus subtilis* which was believed to be a contaminant. The hemoglobin was 15.4 Gm./100 cc., hematocrit 51 per cent, sodium 130, potassium 4.6, carbon dioxide combining power 25.6, and chlorides 104 mEq./L. Systolic blood pressure was maintained at approximately 90 mm. of mercury by means of intravenous norepinephrine and hydrocortisone (100 mg./24 hours), but on the following day the patient lapsed into deep coma. On the sixth postoperative day, blood urea nitrogen rose to 60 mg./100 cc., the patient became anuric, and the blood pressure could no longer be supported with intravenous norepinephrine.

A 22-gage needle was inserted through the abdominal wall and free bile was obtained. Because of the possibility of a bile peritonitis or breakdown of the anastomosis, the abdomen was re-entered under local anesthesia. The anastomotic site was found to be intact and there was no evidence of peritonitis. A transverse loop colostomy was established at this time although the colon was found entirely collapsed. Following this procedure the patient developed a temperature of 104°F. and died without an obtainable blood pressure on the sixth postoperative day.

Dr. Borden: Dr. Cheattle, can you report to us on the surgical specimen?

Dr. Esther Cheattle: Examination of the surgical specimen of colon revealed a 38-cm. segment of large bowel. A 29.5-cm. portion was dilated and the wall was hypertrophied. The remaining 8.5-cm. portion was normal in appearance and was not dilated.

Microscopically all sections of the entire thickness of the colon showed nerve fibers in the usual positions between the layers of the muscularis and in the submucosa. However, in some of the sections ganglion cells could not be demonstrated in sections taken from the dilated resected edge of the specimen (Fig. 3). Ganglion cells were present at the transition zone, and in the normal bowel wall (Fig. 4).

Dr. Borden: In view of this case, I have asked Dr. Smith to review the problems of Hirschsprung's disease.

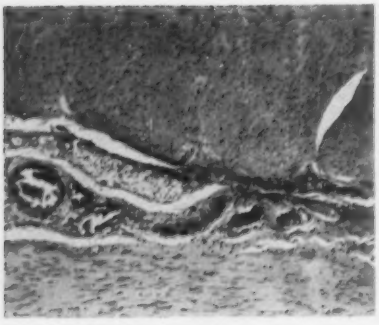

Fig. 3. Aganglionosis.

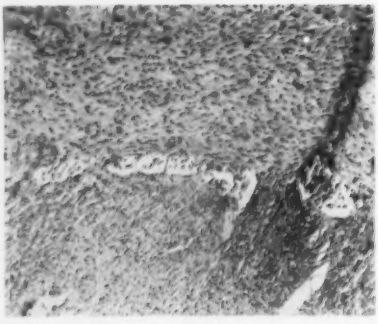

Fig. 4. Ganglion cells.

REVIEW OF TYPES

Dr. Hubbard W. Smith: Hirschsprung's disease, or aganglionic megacolon, is a congenital and familial disorder. It is characterized by constipation dating from birth, massive dilatation and hypertrophy of the colon, and a grossly normal or near normal rectosigmoid. The exact incidence of this disease is unknown but Bodian and co-workers[1] estimate that it occurs once in 30,000 live births. It is predominantly a disease of males.

The term megacolon is a generic name which includes a group of disorders characterized by segmental or total dilatation of the large intestine. There are certain clinical similarities among these which have resulted in the inclusion of many of these cases in the literature on Hirschsprung's disease, and this has confused the subject. Largely through the work of Bodian and co-workers, and of Lee and Bebb,[2] a satisfactory differentiation between the various types has been made which is essential to both clinician and investigator. The clinically distinguishable forms of megacolon are as follows:

Aganglionic Megacolon or Hirschsprung's Disease

Symptoms date from birth in this group. The passage of the first meconium stool is usually delayed for several days. Characteristically there is constipation and obstipation, frequently presenting as an acute intestinal obstruction, within the first few weeks of life. A large percentage of these children die. If they survive the initial bout of obstruction, there follows a long progressive course of recurrent fecal impaction requiring vigorous catharsis and enemas for relief. The abdomen becomes chronically distended with costal flaring. Pain is unusual despite the evidence of obstruction. Rarely, in mild cases, no

significant distention occurs and the constipation is the dominant feature. Bleeding is uncommon. The digital rectal examination and proctoscopy are almost always normal. X-ray characteristically demonstrates a normal or slightly narrowed rectal segment, beyond which is seen a cavernous, dilated, and elongated sigmoid and descending colon.

Organic Megacolon

This type of megacolon is most easily confused with true Hirschsprung's disease. Symptoms are rarely present from birth, but rather begin several months or years later. They can often be traced to coincide with faulty or excessively severe toilet training. Vomiting is rare. Colicky pains are common. The anus is often spastic, and the rectum is dilated and filled with hard feces. On x-ray there is no narrowed segment, but rather the dilatation extends down to the anus.

Nutritional Megacolon

For the sake of completeness one should include the questionable cases of acquired aganglionic megacolon described by Etzel,[3] in which symptoms are similar to those of Hirschsprung's disease but begin sometime after infancy or in adult life. There is no narrowed segment on x-ray. At operation or autopsy there is an absence or paucity of ganglia in the distal dilated colon. It has been suggested that these changes are due to a vitamin deficiency.

HISTORICAL BACKGROUND

Hirschsprung's original description of this disorder is of interest. He stated that "when the abdomen was opened, two enormously dilated loops of large intestine presented themselves—the sigmoid and the even more severely distended transverse colon. Also, the other part of the large intestine appeared somewhat dilated; only the rectum was not enlarged, but rather seemed to be the site of some kind of slight narrowing." Hirschsprung found no gross obstruction and erroneously thought that the dilatation and hypertrophy were the primary congenital disorder. Therapy was for many years directed at this proximal dilated segment.

Various explanations for this disorder have been presented but were found untenable. The possibility that this disorder could be due to some localized anatomic neural lesion was suggested as early as 1901. It was observed that evacuation followed spinal anesthesia in some of these patients and following the work of Tiffin[4] in 1940, it was grad-

ually accepted that Hirschsprung's disease was caused by a congenital absence of the ganglion cells from Meissner's and Auerbach's (myenteric) plexi in the lower sigmoid and/or rectum. According to Bodian's classification this disease is then more properly called "congenital aganglionic megacolon." Whitehouse and Kernohan[5] in 1948 reported 18 cases with aganglionosis. Subsequent reports have brought the total to 267 cases. The aganglionosis is presumably congenital, as such changes have been found in an infant dying at 15 days of age.[1]

PATHOLOGIC FEATURES AND PROCESSES

The gross pathologic picture of megacolon is dominated by great dilatation of the colon with hypertrophy of its musculature. The dilatation extends proximally to a variable point, but usually ends in the transverse colon. Distally the dilated portion narrows in the rectosigmoid to a diameter that is normal or slightly less than normal. The aganglionic segment may measure from 5 to 20 cm. In one series ganglia were absent in the rectum in 100 per cent of cases, in the transition zone in 80 per cent, and in the lower sigmoid in 60 per cent, and in 20 per cent the aganglionosis extended from the rectum into the upper descending colon.[6]

Pathophysiology

The pathophysiology of this disease is now reasonably clear. The myenteric plexus mediates both the extrinsic parasympathetic and the intrinsic control of the activity of the colon.[6] The classical concept of the function of the bowel provides for an inherent propulsive motility even when the bowel is deprived of its external innervation. The sympathetic innervation supposedly has an inhibitory effect, causing retention of fecal contents and retardation of emptying of the colon. The parasympathetic innervation has an augmentative effect which accelerates emptying and causes evacuation of the fecal contents. The basic inherent activity is controlled by the myenteric plexus. Loss of the ganglion cells of this plexus will theoretically result in a decrease in the augmentative effects of the parasympathetic system and possibly in a relative increase in the inhibitory effect of the sympathetic system. More important, perhaps, is the fact that peristalsis cannot take place in the absence of the myenteric plexus.[7]

Abnormal Distal Segment

The distal narrowed segment is abnormal when studied radio-

logically. Uncoordinated and dysrhythmic waves have been observed. Swenson and co-workers[8] demonstrated an increase in "tone" of the narrowed rectal segment using a balloon-manometer technic. They describe either absence of peristalsis or dysrhythmic contractions as the basic defect in rectal motility. From these studies he postulates that in megacolon a delicate balance of pressures develops between the distal nonpropulsive segment and the powerful hypertrophied proximal segment. Initially the proximal segment is able to force feces through the distal segment by dilatation and hypertrophy. When the balance shifts in favor of the distal segment, probably due to hypertrophy of the proximal portion of the nonpropulsive segment in the transition zone, obstipation recurs. Further dilatation must ensue to overcome this obstruction.

Motility studies by Davidson and co-workers[9] showed no difference between the resting activity of colons in normal subjects and in patients with Hirschsprung's disease. They did, however, demonstrate a definite lack of normal response to Mecholyl in the aganglionic segment in 4 of 6 patients with this disorder.

The basic pathologic process in congenital aganglionic megacolon and in cardiospasm (esophageal achalasia) appear to be the same. It was, in fact, because of Lendrum's work on cardiospasm that Robertson and Kernohan reopened the question of aganglionosis in Hirschsprung's disease in 1938. Functional obstructions of the small bowel have been reported in which the obstructing segment was aganglionic and exhibited the typical histologic picture found in Hirschsprung's disease. Ganglionic deficiency may involve other visceral structures besides the gastrointestinal tract. Megaloureter and abnormal bladder function are not infrequent.[10]

MANAGEMENT

Medical

The medical management of congenital aganglionic megacolon has consisted of diet, frequent catharsis, enemas, and the administration of both parasympathomimetic and parasympatholytic drugs. This has been almost uniformly unsuccessful, and the mortality rate has been high, ranging from 19 per cent to 85 per cent. The few reported cases of satisfactory return to normal probably represent cases of functional megacolon rather than true Hirschsprung's disease.

Enemas

Richards and Hiatt[11] have pointed out the potential dangers of

water enemas, particularly when used with neostigmine. They have described the "enema syndrome" which may occur following this procedure, consisting of weakness, headache, emesis, cough, diaphoresis, syncope, peripheral pallor and clamminess, and at times rapid vascular collapse, convulsions, and death. In 42 cases of sudden death in Hirschsprung's disease, this was the apparent cause in 62 per cent. An extracellular fluid dilution takes place due to greatly enhanced water absorption from the large area of the dilated colon, where the fluid is trapped and under increased pressure due to neostigmine. Richards and Hiatt recommend the use of physiologic (0.9%) salt solution or 7% gelatin solutions for enemas or barium suspensions in these cases. Neostigmine, if used at all, should be given in small doses because of the increased sensitivity of the distal spastic segment to parasympathomimetic drugs.

Surgical

Surgical procedures advocated include resection of the dilated portion of the colon, colectomy with or without ileosigmoidostomy, and colostomy. Recurrence of symptoms almost invariably followed the first two procedures. Colostomy gave only temporary relief, with recurrence of symptoms when closed. Sympathectomy was advocated and initially was thought to give good results, but recent follow-up shows most of these cases had recurrences.

Resection of Aganglionic Segment

A more rational approach has followed the recent studies concerning the etiology of Hirschsprung's disease. Surgical resection of the aganglionic segment was first practiced by Swenson,[12] who adapted a pull-through procedure permitting low resection of the rectal segment 1–2 cm. from the anus. More or less simultaneously, other workers, including Bodian, Stephens, and Ward; Ehrenpreis; and Hiatt, developed a technic similar to that of Swenson and differing only in that the narrowed segment was intussuscepted through the anus, permitting the resection and anastamosis to be carried out externally and with less pelvic dissection. Their results compare favorably with those of Swenson. State[13] in 1952 proposed resection of the dilated portion proximally down to and including the narrowed rectal segment, leaving more of the distal rectum. His initial results were almost uniformly good, and a review of 228 cases reported since 1950 reveals a "cure" rate of 94.7 per cent, a surgical mortality of 3.5 per cent, and recurrence in 1.8 per cent. Comparing these results with those obtained by

medical management shows that treatment of this disorder is primarily a surgical problem. The optimal time for operation still must be clarified.

GENERAL DISCUSSION

Dr. Borden: Dr. Texter will open the general discussion.

Dr. E. Clinton Texter, Jr.: Dr. Smith has summarized the natural history of Hirschsprung's disease and in particular the advances of the past few years. I think most of us were unaware of the progress made in surgical treatment during the past 10 years.

The similarity between the mechanisms for cardiospasm and aganglionic megacolon is particularly intriguing. We have not as yet carried out any intraluminal-pressure studies in megacolon, but I have visited Doctors Davidson and Almy and have gone over their tracings. This technic, in addition to its value in understanding the pathophysiology of Hirschsprung's disease, also helps in the diagnosis and treatment of this condition. The "transition" zone can be located quite precisely which is of help to the surgeon.

Several points might be made in relation to the particular patient whose case was reported. His disease was relatively mild; in fact, so mild that he was actually inducted into service for a brief period. Upon admission to the hospital he had no complaints except those referable to the bowel. The x-ray department demonstrated beautifully the narrowed bowel segment. He also had an asymptomatic hydronephrosis which, as Dr. Smith pointed out, is not infrequent in association with aganglionic megacolon.

In view of the reported good results of surgical resection, he was transferred to the surgical service. We were all quite unprepared for the results which followed. The resection was accomplished without difficulty and for a time he appeared to be doing well. About the third postoperative day, his course had started downhill and an x-ray taken on the fourth postoperative day showed free air under the diaphragm. It was thought that perhaps he had leakage at the suture line. Dr. Cailleteau, can you inform us regarding the persistence of pneumoperitoneum after surgery?

Dr. Giles Cailleteau: We have no precise information on that point. Air may persist for several weeks after abdominal surgery. The amount was sufficient to suggest the possibility of a perforated viscus.

Dr. Texter: He continued to be febrile and in shock and died on the sixth postoperative day. Dr. Borden saw him on several occasions during the postoperative period.

Dr. Borden: His picture was primarily one of profound shock complicated by terminal renal shutdown. It was thought that the most likely explanation for this was shock accompanying severe bacteremia. Blood cultures were sterile, however, and he did not respond to measures used to treat shock accompanying bacteremia.

Dr. Texter: Dr. Cheattle will present the autopsy findings.

Autopsy Report

Dr. Cheattle: External examination revealed a recent left paramedian incision 20 cm. in length. A right paramedian incision 13 cm. long with a colostomy was present. There was subcutaneous emphysema of the abdominal wall. Upon opening the peritoneal cavity no free fluid or adhesions were noted. The site of the recent anastomosis in the colon was intact. A round, firm mass weighing 13 Gm. was found at the bifurcation of the aorta which microscopically proved to be a neurofibroma.

There was also another interesting finding at autopsy. The calyces, pelves, and ureters on the right were all dilated. The right kidney weighed 150 Gm., and the cortex was only a little less than average in thickness. No obstructive lesion was demonstrated and the ureters could be followed to their entrance into the urinary bladder.

The right adrenal weighed 24 Gm. Cut section revealed an encapsulated mass $2 \times 2.5 \times 3$ cm., which had a yellowish-tan, moderately firm surface. Yellow adrenal cortex could be seen at the periphery of the mass. The left adrenal was of usual size and appearance, weighing 7 Gm.

Microscopic sections of the adrenal tumor showed nests of large polygonal cells having relatively small round, slightly pleomorphic nuclei diag-

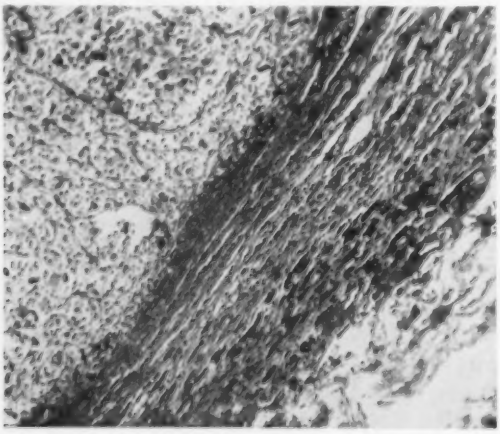

Fig. 5. Section of pheochromocytoma.

nostic of pheochromocytomas (Fig. 5). There is a delicate network of connective tissue between the cells. In many places the cellular arrangement resembles that of the adrenal cortex. A portion of normal adrenal can be seen at the edge of the tumor. A thin fibrous tissue capsule was present.

Dr. David P. Earle, Jr.: The amount of chromatin granules has been used as an index of secretory activity of pheochromocytomas. Was the tumor stained for chromatin granules?

Dr. Cheattle: Yes, it was. Few chromatin granules were present.

Dr. Texter: Hindsight is almost always better than foresight. In reviewing the patient's record after knowledge of the pheochromocytoma, no evidence of previous hypertension was found. He did have an unexplained tachycardia during the anesthesia induction and his blood pressure was low without any obvious reason during surgery. Dr. Smith, in your survey of the literature did you find any similar cases?

Dr. Smith: No, I did not.

Dr. Texter: Unfortunately, all the tumor was fixed so that no assay was possible for either epinephrine or norepinephrine.

Dr. Gene H. Stollerman: It has been previously reported by others, and I can recall one similar situation in my own experience, that a surgical procedure has been complicated by postoperative fatal shock in patients who had an unsuspected pheochromocytoma. I would suspect that this was an actively secreting tumor producing predominantly noradrenalin.

Dr. Borden: Dr. Gilbert has been interested in this problem. Can you help us out?

Dr. Robert P. Gilbert: I could not find any reports of this identical combination. However, two points are worth mentioning: (1) Shock and a fatal outcome have followed relatively minor surgical procedures in patients with pheochromocytoma and (2) in experimental animals one can produce the entity of norepinephrine shock very similar to that shown by this patient.

SUMMARY

1. Hirschsprung's disease, more properly termed "aganglionic megacolon," is a rare congenital disorder.

2. It is characterized by severe constipation, obstipation, and intestinal obstruction.

3. X-ray characteristically demonstrates a normal rectal segment continuous with a cavernous, dilated sigmoid and descending colon.

4. Aganglionic megacolon may be confused with "organic mega-

colon" due to a spastic anal sphincter and with *acquired "nutritional megacolon."*

5. The documented cases of Hirschsprung's disease show congenital absence of the ganglion cells of the Meissner's and Auerbach's plexi in the lower sigmoid and rectum.

6. The pathophysiology is related to the loss of ganglion cells which theoretically results in a decrease in the propulsive effects of the parasympathetic system and an increase in the inhibitory effects of the sympathetic system.

7. Normal peristalsis cannot take place in the absence of the myenteric plexus.

8. Aganglionic megacolon may be associated with other congenital disorders, notably disorders of the urinary tract.

9. Medical management of Hirschsprung's disease is not very satisfactory.

10. The modern surgical technic results in reported "cures" in approximately 95 per cent of patients. The technic consists in resection of the aganglionic segment.

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EDITORIAL

On the Importance of Hirschsprung's Disease and Other Problems

DURING discussions regarding the editorial policy of the *American Journal of Digestive Diseases* the question was raised of whether an editorial board composed of clinicians interested in research could orient the journal so that it would be useful to the practicing physician. In clinical medicine it is almost impossible to separate teaching from research. In the present century, medical teaching has more and more centered about the patient. Osler promoted the concept of bedside teaching and the grand rounds and conference system of teaching was begun. With the increasing size of the group it became necessary to move rounds from the ward to the conference room. In many medical centers the size of the audience has taxed the seating facilities, and it has become apparent that some of these conferences could be presented usefully to a much larger audience than can crowd into a lecture hall.[1]

This "Medical Grand Rounds" on Hirschsprung's disease (see page 35) from the VA Research Hospital-Northwestern University Medical Center illustrates how research may contribute to the management of clinical problems. While the observation by Tiffin *et al.*, and Whitehouse and Kernohan, that the myenteric ganglion cells are absent might not at first have appeared useful, subsequent events have amply demonstrated that it was. Even those who consider that they "keep up with the literature" were surprised at the excellent results now obtained by the surgeons in this condition.

Hirschsprung's disease, or aganglionic megacolon, now appears to be "curable" in a high percentage of patients and falls into the category of rare but curable conditions. The case for more emphasis on these conditions in teaching has been previously emphasized by Levine as follows:

For example, many hours are given to discussions concerning a subject like cancer of the pancreas which is entirely irremediable and too little to tumors of the spinal cord which are often completely curable. The former, of course, is more common, but the latter are more important, because they are amenable to effective treatment. In a word, the first purpose in teaching is that the practicing physician should acquire that information which is directly helpful in the care of the patient.

Of course, research should not be neglected in areas where unsolved problems exist. This is particularly true in gastroenterology where research activity has lagged in relation to the number of unsolved problems. Frequently in research a clear distinction cannot be made between *useful* and *useless* knowledge, and as pointed in the recently reprinted delightful paper by Flexner, ". . . it is an irrational fact that it so often happens that the ceaseless quest for the useless should—sometimes soon and sometimes later—result in conferring some great practical boon upon harassed and floundering mankind."

E. Clinton Texter, Jr., M.D.

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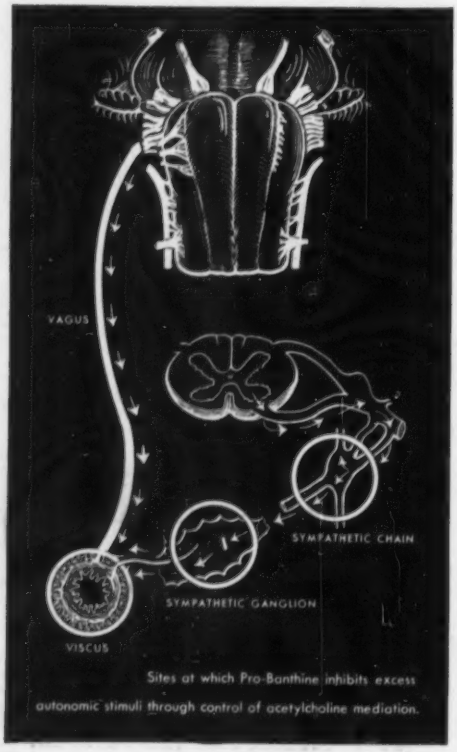
Pro-Banthine is an improved anticholinergic compound. Its unique pharmacologic properties are a decided advance in the control of the most common symptoms of smooth muscle spasm in all segments of the gastrointestinal tract.

By controlling excess motility of the gastrointestinal tract, Pro-Banthine has found wide use[1] in the treatment of peptic ulcer, functional diarrheas and regional enteritis. It is also valuable in the treatment of pylorospasm and spasm of the sphincter of Oddi.



Sites at which Pro-Banthine inhibits excess autonomic stimuli through control of acetylcholine mediation.

Roback and Beal[2] found that Pro-Banthine orally was an "inhibitor of spontaneous and histamine-stimulated gastric secretion" which "resulted in marked and prolonged inhibition of the motility of the stomach, jejunum, and colon . . ."

Therapy with Pro-Banthine is remarkably free from reactions associated with parasympathetic inhibition. Dryness of the mouth and blurred vision are less severe with Pro-Banthine than with certain other potent anticholinergic agents.

In Roback and Beal's[2] series "Side effects were almost entirely absent in single doses of 30 or 40 mg. . . ."

Pro-Banthine Bromide (β-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) is available in sugar-coated tablets of 15 mg.; ampuls of 30 mg., for more rapid effects and in instances when oral medication is impractical or impossible.

For the average patient one tablet of Pro-Banthine (15 mg.) with each meal and two tablets (30 mg.) at bedtime will be adequate. G. D. Searle & Co., Research in the Service of Medicine.

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1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: Gastroenterology *25*:416 (Nov.) 1953.

2. Roback, R. A., and Beal, J. M.: Gastroenterology *25*:24 (Sept.) 1953.

Clinical trial packages of Pro-Banthine and the new booklet, "Case Histories of Anticholinergic Action," are available on request to . . .

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